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### AN ENANTIOSELECTIVE APPROACH TO CARBAPENEM ANTIBIOTICS: FORMAL SYNTHESIS OF (+)-THIENAMYCIN

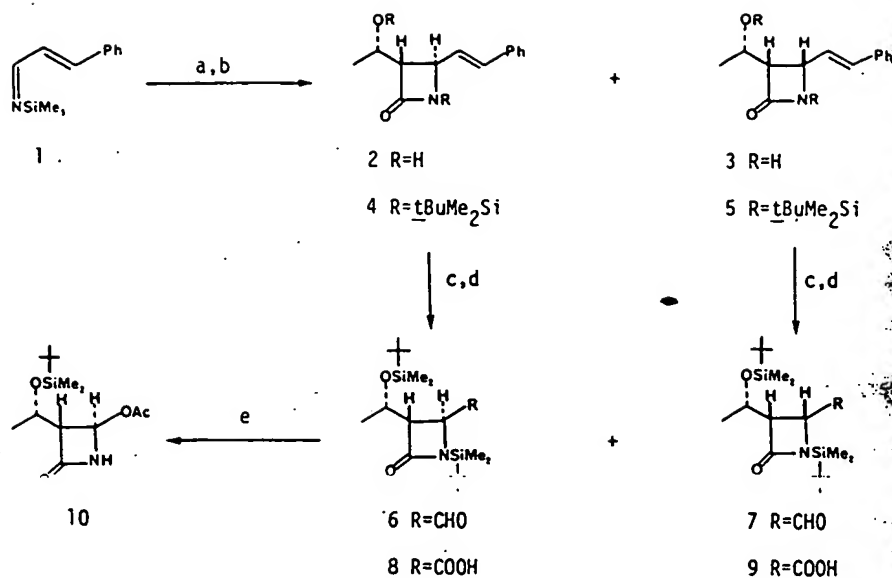
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**Summary:** An enantioselective synthesis of intermediates in syntheses of thienamycin (15) and epithienamycin-C (16) is described.

Several years ago we reported that *N*-trimethylsilyl imines react with ester enolates to form  $\beta$ -lactams as the ester component in this reaction, resulting in a direct route to 3-(1-hydroxyethyl)-2-azetidinones.<sup>2</sup> This letter presents our initial efforts to apply these observations to the area of carbapenem synthesis. Specifically, an efficient enantioselective route to  $\beta$ -lactam 10 and its conversion to the known thienamycin intermediate 14 is described.<sup>3-5</sup> Ethyl (S)-8-hydroxybutyrate<sup>6</sup> was converted to the corresponding dianion (2 equiv LDA, THF, -70°C) and treated with imine 1.<sup>7,8</sup> The resulting crude mixture of  $\beta$ -lactams 2 and 3 was treated with *tert*-butyldimethylsilyl chloride and triethylamine in *N,N*-dimethylformamide<sup>9</sup> to afford 4 (16%) and 5 (27%) after separation by column chromatography. Ozonolysis of 4 gave 6 (85%, mp 131-132°C) and subsequent Jones oxidation afforded acid 8 (86%, mp 105-106°C). Similar oxidative treatment of 5 gave 7 (91%) and 9 (96%, mp 146-147°C). Treatment of either 8 or 9 with lead tetraacetate<sup>10</sup> gave 10 (mp 79-80°C) in 81% and 80% yields, respectively. From an operational standpoint it was most convenient to subject a purified mixture of  $\beta$ -lactams 4 and 5 to the oxidation sequence without purification of the intermediates. In this way, 10 could be prepared from 4 + 5 in a 60% overall yield.

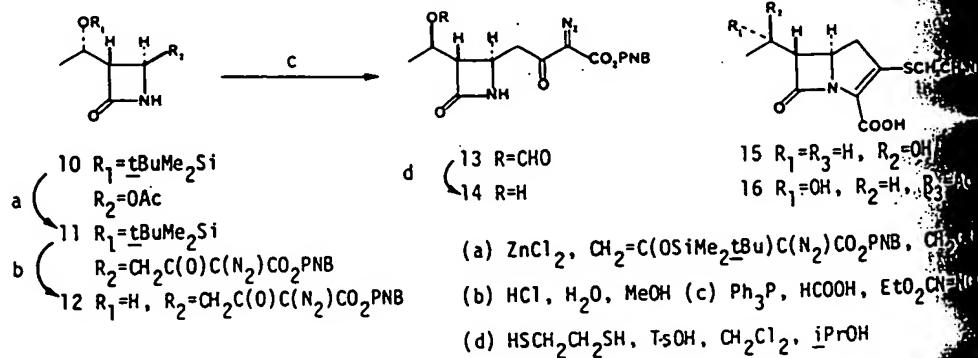
We have demonstrated that 10 will serve as an intermediate in a synthesis of the carbapenem antibiotic thienamycin (15). Thus, treatment of 10 with *p*-nitrobenzyl 2-diazo-3-(*t*-butyldimethylsiloxy)-3-butenolate and ZnCl<sub>2</sub> in dichloromethane gave diazoketone 11 (83%) which was converted to alcohol 12 [95%, mp 150°C (d)] upon exposure to methanol-aqueous hydrochloric acid.<sup>10,12</sup> Inversion of the C-8 stereochemistry was accomplished using the excellent method of Mitsunobu.<sup>13,14</sup> The resulting formate 13 (95%) was converted to the known thienamycin intermediate 14 [87%, mp 151-152°C (lit.<sup>12</sup> 150-152°C)] upon treatment with excess 1,2-ethanedithiol and a catalytic amount of *p*-toluenesulfonic acid in dichloromethane-isopropanol (25°C, 96h), thus completing a formal total synthesis of thienamycin (15).<sup>14,15</sup> The use of 12 in a synthesis of the related carbapenem antibiotic epithienamycin-C (MM22381, 16) will appear in our full account of this work.



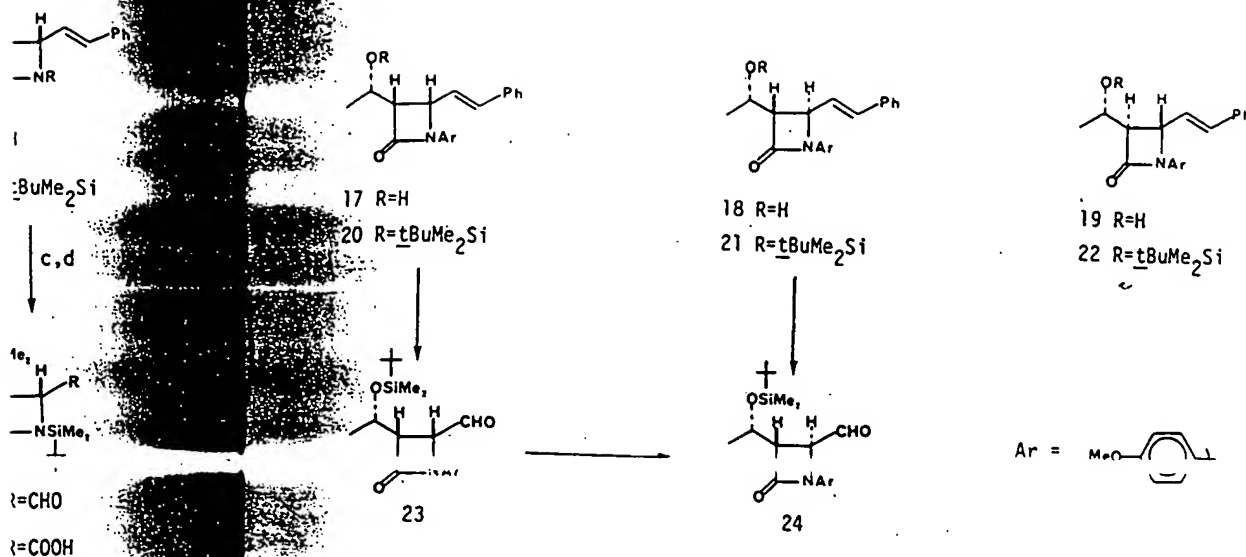
(a) CH<sub>3</sub>CH(OLi)CH=C(OEt)(OLi), THF, -70°C → 25°C, 20h (b) tBuMe<sub>2</sub>SiCl, Et<sub>3</sub>N, DMF

(c) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78°C then Me<sub>2</sub>S (d) Jones Reagent (e) Pb(OAc)<sub>4</sub>, AcOH

We have also examined the behavior of the dianion of ethyl β-hydroxybutyrate with N-p-methoxyphenylaldimines. A few of our results are reported here. Treatment of N-p-methoxyphenylcinnamaldimine with the dianion of ethyl β-hydroxybutyrate in tetrahydrofuran (-70°C, then 20h at room temperature) afforded a mixture of 17 (25%, mp 160-161°C) and 18 + 19 (38%, respectively).<sup>16</sup> Silylation<sup>9</sup> of the mixture of 18 + 19 gave 21 (72%, mp 97-98°C) and 22 (23%, mp 124-125°C) after separation by chromatography. The stereochemical assignment for 21 was established by sequential silylation to give 20 (88%), ceric ammonium nitrate oxidation,<sup>17</sup> and silylation to give 5 (78%). The stereochemical assignments for the trans β-lactams were confirmed by converting both 20 and 21 to 24. Thus, ozonolysis of 21 gave 21 (86%, mp 113-115°C) and ozonolysis of 20 (90%) followed by epimerization (DBU, CH<sub>2</sub>Cl<sub>2</sub>, 25°C).



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7-98°C) and 22  
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DBU, CH<sub>2</sub>Cl<sub>2</sub>, 25°C

R<sub>3</sub>=H, R<sub>2</sub>=OH  
=OH, R<sub>2</sub>=H, R<sub>3</sub>=  
(N<sub>2</sub>)CO<sub>2</sub>PNB, CH<sub>3</sub>  
HCOOH, EtO<sub>2</sub>CN=H  
iPrOH

Sh) of the resulting aldehyde 23 (mp 79.5-80.5°C) also gave 24 (88%).<sup>18</sup> It is notable that we have not been able to isomerize 7 to 6 under identical conditions.

In summary, we have shown that the ester-imine condensation can be included in the list of enantioselective routes to carbapenem intermediates. The methods and intermediates described herein should also be useful in the synthesis of analogs such as carbacephems.

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18. Aldehyde 23 was also isolated in 9% yield.

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